

**REMARKS**

**A. The Amendments and the Status of the Claims**

Claims 100, 127, 210, 212, 213, 310, and 412 have been amended to define the Applicants' invention with more precision and particularity. Claims 103, and 214-216 have been canceled without prejudice. The claims, as amended, are supported by the specification and the original claims. In particular, the limitation reciting a membrane that is "free of disulfide linkages" is disclosed on page 16, lines 1-2 of the originally filed application. Accordingly, the present amendment has added no new matter.

**B. Rejection Under 35 U.S.C. § 112, Second Paragraph**

Claim 103 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. By the present amendment, claim 103 has been canceled without prejudice; therefore, the rejection is moot. Accordingly, the withdrawal of the rejection is respectfully requested.

**C. First Rejection Under 35 U.S.C. § 103(a)**

In item 3 on page 3 of the Office Action, the Examiner rejected claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, and 412 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Grinstaff (U.S. Patent No. 5,498,421) in view of Wallach (U.S. Patent No. 4,853,228), Allen (U.S. Patent No. 5,620,689), Glajch (U.S. Patent No. 5,147,631), and Quay (U.S. Patent No. 5,409,688). The rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the following three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference(s)

as proposed by the Examiner; (2) there must be a reasonable expectation of success and (3) the prior art reference(s) must teach or suggest all of the claim limitations. The Applicants respectfully submit that none of the criteria has been satisfied in this case because none of the cited references, either alone or in combination, disclose or suggest every limitation of claims 100, 127, and 412.

Each of claims 100, 127, and 412, as amended, recites vesicles having a membrane that is “free of disulfide linkages.” The references cited by the Examiner do not disclose such a limitation.

In particular, the principal reference, Grinstaff, describes encapsulation of various substances in polymeric shells to form microbubbles that are used for in vivo delivery of many therapeutic or diagnostic agents. Grinstaff fails to teach that the polymeric shells that are used are “free of disulfide linkages,” as required by claims 100, 127, and 412. None of the other cited references (i.e., Wallach, Allen, Glajch, or Quay) cures this deficiency. Wallach and Allen describe the use of lipid vesicles, e.g., liposomes, and Glajch and Quay disclose the use of perfluorocarbons, but fail to describe or suggest the polymeric shells free of disulfide links.

Thus, the combination of these five references fails to describe every limitation of claims 100, 127, and 412. Nor is there any suggestion that would motivate one having ordinary skill in the art to modify what is described in Grinstaff to arrive to the vesicles free of disulfide linkages. To the contrary, Grinstaff actually teaches away from using the shells free of disulfide linkages, by requiring that the polymeric shells are made of cross-linked polymers, where the cross-linking is achieved by forming the disulfide bonds. The requirement of the cross-linking with disulfide bonds is present throughout the entire Grinstaff reference (see, e.g., Grinstaff, Col. 6, lines 14-15; Col. 7, line 32; Col. 8, lines 12-13; and claim 1). Clearly, there is no motivation to avoid the presence of disulfide linkages when the principal reference requires the use of such linkages.

Accordingly, it is respectfully submitted that claims 100, 127 and 412 are patentably distinguishable over the references cited by the Examiner. All other claims depend, directly or indirectly, on either claim 100 or claim 127, and are allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

**D. Second Rejection Under 35 U.S.C. § 103(a)**

In Item 4 on page 6 of the Office Action, the Examiner rejected claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, and 412 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wallach and Allen in view of Schneider (U.S. Patent No. 5,643,553) and Porter (U.S. Patent No. 5,648,098). The rejection is respectfully traversed because these references cannot be properly combined.

Each of claims 100, 127, and 412, as amended, recites vesicles having a “solid” membrane. The references cited by the Examiner do not disclose such a limitation.

It is submitted that the Examiner seems to have misunderstood the argument previously set forth by the Applicants. The Applicants never disputed that the Schneider reference describes microbubbles comprising a gas, and previously agreed, and still agree, with such characterization. The Applicants previously pointed out that Schneider describes the microbubbles as air or gas globules suspended in a liquid (Col. 1, lines 25-26). This is still correct, and the Applicants’ view on this is the same as the Examiner’s view.

However, in order to be a proper reference, Schneider must disclose the vesicles having a solid membrane encapsulating a gas. The solid membrane limitation is not taught by Schneider. All that is disclosed by Schneider is microbubbles having the gas/liquid interface. There is no solid membrane anywhere in Schneider.

Short of the direct teaching, alternatively, there must be a suggestion or motivation in Schneider or in any combination of Schneider, Wallach, Allen and Porter to modify what is described in Schneider to include the solid membrane limitation. It is submitted that there is no such suggestion or motivation. Indeed, as previously pointed out by the Applicants, Schneider actually teaches away from using the microcapsules having "a gas entrapped inside solid membrane vesicles" (Col. 3, lines 38-40) by emphasizing that the microcapsules having solid membrane are so different from the microbubbles (having no solid membrane) that they "belong to a different kind of art" (Col. 3, line 41). Schneider is concerned exclusively with the microbubbles without the solid membrane.

It can be, therefore, concluded that Schneider, alone or in combination with Wallach, Allen, and Porter, neither teaches nor suggests using the gas-filled vesicles having a solid membrane recited in claims 100, 127, and 412. Accordingly, it is respectfully submitted that claims 100, 127 and 412 are patentably distinguishable over the combination of Wallach, Allen, Schneider, and Porter cited by the Examiner. All other claims depend, directly or indirectly, on either claim 100 or claim 127, and are allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

**E. Third Rejection Under 35 U.S.C. § 103(a)**

In Item 6 on page 7 of the Office Action, the Examiner rejected claims 100, 102-103, 127, 194-200, 203, 210-220, 294-300, 303, 310-317, 326-337, 347-350, and 412 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Grinstaff in view of Wallach, Allen, Glajch, Quay and further in view of Ginsburg (U.S. Patent No. 5,656,442). The rejection is respectfully traversed.

The teachings of Grinstaff, Wallach, Allen, Glajch, and Quay are described above. As mentioned above, none of these five references, nor any combination thereof, teaches or suggests using vesicles having a membrane that is "free of disulfide linkages,"

as recited by claims 100, 127, and 412. Ginsburg fails to cure this deficiency. Ginsburg only describes specific targeting agent but does not disclose using a membrane free of disulfide linkages nor suggests the modification of Grinstaff to include the “free of disulfide linkages” limitation.

Accordingly, it is respectfully submitted that claims 100, 127 and 412 are patentably distinguishable over the combination of Grinstaff, Wallach, Allen, Glajch, Quay, and Ginsburg. All other claims depend, directly or indirectly, on either claim 100 or claim 127, and are allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

**F. Fourth Rejection Under 35 U.S.C. § 103(a)**

In Item 7 on page 8 of the Office Action, the Examiner rejected claims 100, 102-103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, and 412 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wallach and Allen in view of Schneider and Porter, and further in view of Ginsburg. The rejection is respectfully traversed.

The teachings of Wallach, Allen, Schneider and Porter are described above. As mentioned above, none of these references, nor any combination thereof, teaches or suggests using the gas-filled vesicles having a solid membrane recited in claims 100, 127, and 412. Ginsburg fails to cure this deficiency. As mentioned above, Ginsburg describes specific targeting agent but does not disclose using a solid membrane.

Accordingly, it is respectfully submitted that claims 100, 127 and 412 are patentably distinguishable over the combination of Wallach, Allen, Schneider, Porter, and Ginsburg. All other claims depend, directly or indirectly, on either claim 100 or claim 127, and are allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

In re Application of:  
Unger et al.  
Application No.: 09/218,660  
Filed: December 22, 1998  
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PATENT  
Attorney Docket No.: IMARX1100-3

**CONCLUSION**

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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